Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 15-19 are pending in the application, with 15 and 18 being the independent claims.

Based on the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn or held in abeyance as indicated below.

Cross Reference to Related Applications

The Cross-Reference to Related Applications has been amended to update the status of certain of the priority documents.

Substitute Sequence Listing

The substitute sequence listing filed May 28, 2002, contains an error. Specifically, Applicant inadvertently submitted the base sequence of GLP-1 (7-36) but containing a leucine rather than an isoleucine at position 29 of GLP-1 (1-37). Applicant intended to use GLP-1 (7-37) as the base sequence. A substitute sequence listing correcting this error will be submitted shortly.

Summary of the Office Action

In the Office Action date August 28, 2002, the Examiner has made three rejections of the claims. Applicant respectfully offer the following remarks to overcome, traverse, or accommodate these rejections.

Rejections under 35 U.S.C. § 112, First Paragraph

In the Office Action at page 3, number 4, the Examiner has rejected claims 15-19, under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, to make and/or use the invention. Applicant respectfully traverses this rejection in view of the following remarks.

The Applicant respectfully points out that the Examiner has misread the pending claims, specifically claims 15 and 18. Claim 15 states:

> A derivative of glucagon-like peptide 1 (7-37), (GLP-1 (7-37)), wherein the amino acid sequence of said derivative has the same number of amino acids as said GLP-1 (7-37), and at least 80% amino acid identity to said GLP-1 (7-37), and wherein said derivative has an insulinotropic activity that exceeds the insulinotropic activity of GLP-1 (1-37) and GLP-1 (1-36). (Emphasis added)

Claim 15, U.S. Pat. Application No. 09/635,679.

Specifically, the Examiner asserts in the Office Action at page 3, part 4, lines 9-12, that the "specification teaches one skill of in the art how to make the claimed derivative; however not the characteristics (said derivative has an insulinotropic activity that exceeds the insulinotropic activity of GLP-1 (1-37) and GLP-1 (7-37)) (emphasis added) and how to use the claimed derivative."

Claim 15 refers to GLP-1 (1-37) and GLP-1 (1-36), not GLP-1 (7-37), as stated by the Examiner. Example 5 at page 30, lines 11-12, discloses that GLP-1 (7-37) is more than 1,000-fold more potent than GLP-1 (1-37) in stimulating insulin expression.

The Examiner relies on Drucker as evidence Applicant's derivative would not be active. However, Drucker tested GLP-1(1-36)-NH_2. The reason Drucker's compound only weakly stimulated insulin release was because it contained GLP-1 amino acids 1-6. As claimed, the insulinotropic activity of our derivative exceeds the insulinotropic activity of GLP-1 (1-36). We have taught the art that amino acids 1-6 depress the insulinotropic activity. The artisan who read Drucker would immediately see that amino acids 1-6 are present in Drucker's compound. Accordingly, Drucker does not detract from the enablement of the claimed invention.

Prima facie nonenablement is not established. While it is true that Applicant does not have an example in which he made the selected species and demonstrated that it is active, such an example is not needed. The Examiner provided no evidence that the isoleucine at position 29 is in a critical insulinotropic position. Leucine and isoleucine are both hydrophobic and are often substituted for each other. (See **Exhibit 1**, and below). The skilled artisan would expect that a GLP-1 derivative in which leucine is substituted for isoleucine would be active.

In fact, *Mojsov, Role of GLP-1 (7-37) in Insulin Secretion*, NIH Grant Application (May, 1987), shows a sequence alignment of mammalian GLP-1(7-37) sequence with various fish GLP-1 sequences, demonstrating the tolerance of an amino acid substitution at position 29 of GLP-1 (7-37). See pg 25 of *Mosjov* **(Exhibit 2.)** (In *Mosjov*, mammalian GLP-1 is incorrectly numbered, position 29 is mislabeled as position 28). This alignment demonstrates that fish GLP-1's tolerate, and remain active, with an amino acid substitution of valine for isoleucine at position 23 in the fish sequence, which corresponds to position 29 of mammalian GLP-1 (7-37).

The United States Patent and Trademark Office bears the initial burden of proving that a specification is non-enabling. A specification is presumed to be enabling unless the Examiner

proves acceptable objective evidence or sound scientific reasoning showing that it would require undue experimentation. Applicant respectfully asserts that this burden has not been met in the present case, or, if it has been met, that Applicant has provided good and sufficient evidence to overcome the same. The present application teaches one skilled in the art to make and use the invention as claimed.

In view of the forgoing remarks, Applicant respectfully assets that the specification as originally filed fully enables the invention as presently claimed. Hence, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejections under 35 U.S.C. § 102(a)

In the Office Action at page 4, number 6, the Examiner has rejected to claims 15-19, under 35 U.S.C. § 102(a) as allegedly being anticipated by *Komatsu et al.*, Biomed. Res., 9(Suppl. 3):201-206, Biomedical Research Foundation (1988) or *Mojsov*. Applicant respectfully traverse this rejection.

As the Examiner points out, *Komatsu et al.* discloses a truncated derivative of GLP-1 (7-37), GLP-1 (7-36). See Office Action at part 4, page 4, lines 3-4; see also *Komatsu et al. Biomed. Research* 9, Supplement 3, 201-206, 1988. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); see also MPEP 2131. It is the Applicant's contention that this disclosure does not anticipate the invention as claimed. The claims are directed to derivatives of GLP-1 (7-37), "wherein the amino acid sequence of said derivative has the same

number of amino acids as said GLP-1 (7-37), and wherein said derivative has insulinotropic activity that exceeds the insulinotrpoic activity of GLP-1 (1-37) and GLP-1 (1-36)." (Emphasis added). See Claims 15 and 18. Thus, as claimed, the invention does not claim truncated derivatives, and therefore, the invention as claimed is not anticipated by *Komatsu et al.*

The Examiner also alleges that the invention as claimed is anticipated by Dr. Mojsov's 1987 NIH Grant Application. Applicant respectfully requests that this rejection be held in abeyance pending completion of an inventorship determination as discussed below in the section addressing the rejection under 35 U.S.C. §102 (f).

In view of the forgoing remarks, Applicant respectfully contends that *Komatsu et al.* does not anticipate the claimed invention. Hence, reconsideration and withdrawal of *Komatsu et al.* rejection are respectfully requested.

Rejections under 35 U.S.C. § 102(f)

In the Office Action at page 5, part 7, the Examiner has rejected to claims 15-19, under 35 U.S.C. § 102(f), alleging that the Applicant did not invent the claimed subject matter.

Mosjov does not raise a presumption that Dr. Mosjov is an inventor or co-inventor of the subject matter as claimed. However, in the interests of ensuring that inventorship is correct, an inventorship determination is being conducted. Applicant is investigating whether Dr. Mojsov is an inventor or coinventor of any of the claims in this application. This investigation is still ongoing. Applicant will advise the United States Patent and Trademark Office of the results of this investigation as soon as it is complete. Therefore, Applicant respectfully requests that this rejection be put in abeyance until such time that the inventorship investigation is complete.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant notes that the question of whether Dr. Morjov is an inventor or coinventor is still under investigation. Therefore, Applicant believe that a full and complete reply has been made to the outstanding Office Action. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

This application is a continuation of U.S. Application No. 09/090,949, filed June 5, 19[8]98, which is a continuation of U.S. Application No. 08/749,762, filed November 20, 1996, Pat. No. U.S. 5,958,909, which is a continuation of U.S. Application No. 08/156,800, filed November 23, 1993, Pat. No. 5,614,492, which is a continuation of U.S. Application No. 07/756,215, filed September 5, 1991, abandoned, which is a continuation-in-part of United States Patent Application No. 07/532,111, filed June 1, 1990, Pat. No. 5,118,666, which is a [file wrapper] continuation of U.S. Application No. 07/148,517, filed January 26, 1988, abandoned, which is a continuation-in-part of U.S. Application No. 06/859,928, filed on May 5, 1986, [and is now] abandoned.